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| EXAMINER | |
|---|---|
| KISHORE, GOLLAMUDI S | |
| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/723,423 | JENSEN ET AL. | |
| | Examiner | Art Unit | |
| | Gollamudi S. Kishore | 1612 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *24-30 and 39-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-30 and 39-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

The amendment dated 3-9-09 is acknowledged.

Claims included in the prosecution are 24-30 and 39-63.

Upon consideration, the 103 rejection of claims over Lopez-Berestein by itself or in combination with Allen, Fujii and O'Rear is withdrawn.

### *Claim Rejections - 35 USC § 112*

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 24-30 and 39-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is confusing. It recites two functional limitations 1 and 2, which contradict each other in terms of half-life. The same is the case with the other independent claims.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant once again argues that the specification shows two embodiments and in one embodiment, the invention provides agents encapsulated in liposomes that provide an elimination half-life that is at least as great as the value of the free drug, and an upper value of less than 14 hours. This argument is not persuasive since as pointed out before, ***the claims recite on specific composition and therefore, only one elimination time is possible.*** If applicant intended to convey that the elimination time is less than 14 hours, then applicant should have recited only this function and not both.

Furthermore, if the elimination half time of an encapsulated compound is the same as an unencapsulated compound, then what is the point in encapsulating the compound? The rejection is maintained.

***Claim Rejections - 35 USC § 103***

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 24-30 and 39-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hersch (5,759,571) by itself or in combination with Allen (BBA), Fujii (5,328,678), O'Rear (5,503,850) individually or in combination.

Hersch discloses liposomes containing amino glycoside, amikacin. The liposomal formulations contain various claimed neutral phospholipids, hydrogenated soy phosphatidylcholine (HSPC, DMPC, DSPC, DPPC, anionic phospholipids and cholesterol, in particular HSPC and DSPG and cholesterol in claimed ratios. The lipid-drug ratios fall within the claimed amounts. The liposomal sizes are less than 100 nm. The method disclosed includes IV injection into mice. The method also includes patients (humans) (abstract; col. 3, line 65 through col. 6, line 63; Examples and claims). Hersch does not teach all of the claimed ratios with respect to the phospholipids and cholesterol and the lipid and the drug. However, in the absence of showing unexpected results, it is

deemed obvious to one of ordinary skill in the art to vary the amounts of the lipids, cholesterol and drug from the guidance provided by Hersch to obtain the best possible results. Hersch also does not teach the encapsulation of anti-cancer drugs such as cisplatin. However, since the principle of encapsulation is the same, one of ordinary skill in the art would be motivated to encapsulate cisplatin if the desired goal is to treat cancer.

Allen teaches that the presence of serum significantly increased liposome leakage and the incorporation of increasing molar ratios of cholesterol into liposomes was required to reduce the leakage of calcein (active agent) from the liposomes incubated with buffer and with serum (Summary, Tables and Figures). This implies that the active agent from liposomes without cholesterol will leak and release the active agent quickly as opposed to liposomes with increasing amounts of cholesterol.

Fujii teaches that sterols such as cholesterol help stabilize the bilayer toward leakage and destruction in the plasma (col. 3, lines 5-10).

O'Rear teaches that various liposomes can be selected for the desired characteristics or manipulated to produce the desired characteristics and solute retention by liposomes and their half-life in the circulation can be controlled by appropriate manipulation of the liposomal membrane fluidity and composition. O'Rear further teaches that in the absence of cholesterol, liposomes may leak substantially when introduced intravenously and that cholesterol alters the mechanical and structural properties of the phospholipid bilayer of the liposome to cause variable permeability and fragility (col. 3, line 58 through col. 4, line 5).

Assuming that the cholesterol amounts in Hersch with respect to other phospholipids are different from instant amounts, it would have been obvious to one of ordinary skill in the art to decrease its amounts if quicker release of the active agent in the blood is desired based on the teachings of Allen, Fujii and O'Rear. Thus, the selection of appropriate phospholipid and manipulating the amounts of cholesterol would have been obvious based on the teachings of O'Rear.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Hersch at col. 6, lines 11-17 recites liposomes with a preferred ratio of HSPC:cholesterol:DSPG of about 2:1:0.1 and the drug to total lipid ratio of about 1:4 and that the office action has provided no text reference or knowledge why the above ratio suggest an HSPC:cholesterol:DSPG ratio of 4:1:0.1 as recited in claim 24. This argument is not persuasive since at the same location, Hersch teaches "Other preferred formulations include DSPG in a molar amount ***of 0*** to 20 % and most preferably in a molar amount ***of less than 5*** %. Therefore, one of ordinary skill in the art would be motivated to vary the amounts of DSPG in the liposomal formulations in order to obtain the best possible results. Furthermore, according to one of the limitations of instant claims, the elimination half-life of the therapeutic agent is at least as long as the elimination half-life of the therapeutic agent when administered in the absence of liposome, which implies no criticality of the liposomal encapsulation of that therapeutic agent at all. Applicant points out to Example 5 (Table 5) of Hersch and argue that Hersch reports that liposomes prepared therein provide a significant plasma concentration of amikacin at 14 and 24 hr after administration and thus, when

considered alone, Hersch teaches away from claims 24-30 and 39-58. These arguments are not persuasive. First of all, instant specification there is no specific definition for the term, 'elimination half-time". Half life is generally defined as the time it takes for half of a material to disappear. Based on that definition, it is unclear as to how one can interpret the results in Table 5 of Hersch as different from instant results. Furthermore, half life of a drug depends upon the nature of the drug and the amount of drug administered and instant claims do not recite any specific drugs or their amounts.

5. Claims 24-30 and 39- 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lopez-Berestein (5,032,404) by itself or in combination with Allen (BBA), Fujii (5,328,678), and O'Rear (5,503,850) individually or in combination, further in view of Hersch (5,759,571).

Lopez-Berestein discloses liposomes containing polyene antibiotics which include amikacin. The liposomal formulations contain various claimed phospholipids and cholesterol. The phospholipids include DSPC, DEPC, DMPC, DOPC and phosphatidylglycerols. The liposomes are either unilamellar or multilamellar. The liposomes are administered parenterally. The lipid-drug ratios and the lipid-cholesterol ratios disclosed by Lopez-Berestein fall within the claimed ratios (abstract; col. 7, line 49 through col. 8, line 13; col. 8, lines 34-66; col. 9, lines 15-47; Table 5; Examples, in particular Example 3, 15 and claims).. According to Lopez-Berestein the compositions include Cholesterol in concentrations from 10 to 75 weight percentages. The amounts of phospholipids (10 mg) and cholesterol (3, 2 and 1 mg) when expressed in molar amounts appear to be closer to the 4:1:0.1 ratios of HSPC, cholesterol and DSPG in

instant claim 1. In view of Lopez-Bernstein's teachings of the claimed phospholipids and the suggestion that the amounts of cholesterol can be varied from 10 to 75 weight percentages, it would have been obvious to one of ordinary skill in the art to select a phospholipid and vary the amount of cholesterol from the teachings of Lopez-Berestein with the expectation of obtaining the best possible results. Although Lopez-Berestein in examples uses DMPG, in view of his generic teachings of the use of phosphatidylglycerols, one would be motivated to use a specific phosphatidylglycerol such as DSPG with a reasonable expectation of success. Lopez-Berestein does not teach the encapsulation of anti-cancer drugs such as cisplatin. However, since the principle of encapsulation is the same, one of ordinary skill in the art would be motivated to encapsulate cisplatin if the desired goal is to treat cancer.

Allen teaches that the presence of serum significantly increased liposome leakage and the incorporation of increasing molar ratios of cholesterol into liposomes was required to reduce the leakage of calcein (active agent) from the liposomes incubated with buffer and with serum (Summary, Tables and Figures). This implies that the active agent from liposomes without cholesterol will leak and release the active agent quickly as opposed to liposomes with increasing amounts of cholesterol.

Fujii teaches that sterols such as cholesterol help stabilize the bilayer toward leakage and destruction in the plasma (col. 3, lines 5-10).

O'Rear teaches that various liposomes can be selected for the desired characteristics or manipulated to produce the desired characteristics and solute retention by liposomes and their half-life in the circulation can be controlled by

appropriate manipulation of the liposomal membrane fluidity and composition. O'Rear further teaches that in the absence of cholesterol, liposomes may leak substantially when introduced intravenously and that cholesterol alters the mechanical and structural properties of the phospholipid bilayer of the liposome to cause variable permeability and fragility (col. 3, line 58 through col. 4, line 5).

Assuming that the cholesterol amounts in Lopez-Berestein are different from instant amounts, it would have been obvious to one of ordinary skill in the art to decrease its amounts if quicker release of the active agent in the blood is desired based on the teachings of Allen, Fujii and O'Rear. Thus, the selection of appropriate phospholipid and manipulating the amounts of cholesterol would have been obvious based on the teachings of O'Rear. Although, the amounts of phosphatidylglycerol in Lopez-Berestein are higher, one of ordinary skill in the art would be motivated to change the amounts in view of Hersch's teachings that the amounts of phosphatidylglycerol can be varied from 0 to 20 %. As pointed out above, Lopez-Berestein teaches generic phosphatidylglycerol, but not specific species such as distearoylphosphatidylglycerol (DSPG). As also pointed out above, Hersch teaches DSPG as a preferred phospholipid in combination with phosphatidylcholine. Therefore, it would have been obvious to one of ordinary skill in the art to use DSPG taught by Hersch as the specific PG in Lopez-Berestein with a reasonable expectation of success. Alternately, to include a phosphatidylcholine such as DEPC in Hersch would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since Lopez-Berestein

teaches that this phosphatidylcholine could be used in combination with phosphatidylglycerol.

Applicant's arguments have been fully considered, but are not persuasive. Applicant once again argues regarding the amounts DSPG and the ratios of HSPC to DSPG in Lopez-Berestein. These arguments are not persuasive since it is within the skill of the art to vary the amounts of the anionic phospholipid with the expectation of obtaining the best possible results. Furthermore, as pointed out above, Hersch teaches that the amounts of phosphatidylglycerol can be varied from 0 to 20 %.

6. Claims 29 and 44-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lopez-Berestein, Allen (BBA), Fujii (5,328,678), and O'Rear (5,503,850) individually or in combination and Hersch; OR Hersch, Allen (BBA), Fujii (5,328,678), O'Rear (5,503,850) individually or in combination also as set forth above, further in view of Abra (5,945,122).

The teachings of Lopez-Berestein and Hersch, Allen (BBA), Fujii (5,328,678), O'Rear (5,503,850) have been discussed above. What is lacking in these references is the teaching that the active is anti-neoplastic agent such as cisplatin.

Abra as pointed out before teaches liposomal encapsulation of cisplatin. It would have been obvious to one of ordinary skill in the art to encapsulate cisplatin in the liposomes of Lopez-Berestein or Hersch with a reasonable expectation of similar encapsulation since the reference of Abra shows that this compound is routinely encapsulated in liposomes for cancer treatment.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that Abra states on col. 1, lines 63-67 that cisplatin is difficult to efficiently entrap in liposomes because of the drug's low aqueous solubility, approximately 1.0 mg/ml at room temperature and low lipophilicity, both of which contribute to a low drug/lipid ratio and thus, Abra teaches away from claim 29. The rationale behind this argument is not readily apparent to the examiner since Abra's invention is concerned with encapsulation of cisplatin in liposomes. Furthermore, instant claim does not recite any amounts for cisplatin and therefore, this argument is not persuasive.

7. Claims 25-26, 28, 40, 41, 43, 55-56, 58-61 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayes (5,869,092) by itself or in combination with Hersch (5,759,571), Allen (BBA), Fujii (5,328,678), O'Rear (5,503,850) individually or in combination..

According to instant claim 25, the liposomes comprise DEPC and cholesterol in a ratio of about 2:1.

Hayes teaches liposomal compositions containing dielaidoylphosphatidylcholine (abstract, col. 9, line 36; examples 2 and 3). According to Hayes cholesterol can be present in amounts from 0.1 to 1.0 mole ratio (col. 8, lines 4-9). The liposomes encapsulate a lipophilic drug (col. 8, lines 40-56). According to Hayes, the phospholipid can be either DEPC or DMPC (claim 12). . Further according to Hayes, the liposomes can further include negatively charged phospholipids and the choice of the lipid is generally based on such factors as the desired size and stability of the resulting

liposomes in the blood stream or other intended mode of administration (col. 7, lines 45-52). The inclusion of cholesterol in instant amounts in DEPC liposomes would have been obvious to one of ordinary skill in the art since Hayes is suggestive of the inclusion of cholesterol from 0.1 to 1 mole ratios with the phospholipid. The inclusion of a negatively charged phospholipid such as phosphatidylglycerol (DSPG) would have been obvious to one of ordinary skill in the art since Hayes is suggestive of such an inclusion. Although Hayes does not teach instant amounts of phosphatidylglycerol, in the absence of showing the criticality, it is deemed obvious to one of ordinary skill in the art to manipulate the amounts to obtain the best possible results.

Hersch discloses liposomes containing amino glycoside, amikacin. The liposomal formulations contain various claimed neutral phospholipids DMPC, DSPC, DPPC, anionic phospholipids and cholesterol, in particular HSPC, cholesterol and DSPG in a ratio of 2:1: 01. The lipid-drug ratios fall within the claimed amounts. The liposomal sizes are less than 100 nm. The method disclosed includes IV injection into mice. The method also includes patients (humans) (abstract; col. 3, line 65 through col. 6, line 63; Examples and claims).

Allen teaches that the presence of serum significantly increased liposome leakage and the incorporation of increasing molar ratios of cholesterol into liposomes was required to reduce the leakage of calcein (active agent) from the liposomes incubated with buffer and with serum (Summary, Tables and Figures). This implies that the active agent from liposomes without cholesterol will leak and release the active agent quickly as opposed to liposomes with increasing amounts of cholesterol.

Fujii teaches that sterols such as cholesterol help stabilize the bilayer toward leakage and destruction in the plasma (col. 3, lines 5-10).

O'Rear teaches that various liposomes can be selected for the desired characteristics or manipulated to produce the desired characteristics and solute retention by liposomes and their half-life in the circulation can be controlled by appropriate manipulation of the liposomal membrane fluidity and composition. O'Rear further teaches that in the absence of cholesterol, liposomes may leak substantially when introduced intravenously and that cholesterol alters the mechanical and structural properties of the phospholipid bilayer of the liposome to cause variable permeability and fragility (col. 3, line 58 through col. 4, line 5).

Assuming that the cholesterol amounts in Hayes with respect to other phospholipids are different from instant amounts, it would have been obvious to one of ordinary skill in the art to decrease its amounts based on the teachings of Hersch and if quicker release of the active agent in the blood is desired, based on the teachings of Allen, Fujii and O'Rear. Thus, the selection of appropriate phospholipid and manipulating the amounts of cholesterol would have been obvious based on the teachings of O'Rear.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that Hays describe(s) liposome systems that are very different than the liposomes recited in instant claims and that liposomes described by Hays would not provide liposomes with intermediate release properties. This argument is not persuasive since instant claims are composition claims and not method claims and Hays teaches

the formation of liposomes using the claimed DEPC and cholesterol and Hays is further suggestive of the inclusion of a negatively charged lipid. Thus, applicant's arguments that Hays would not provide liposomes with intermediate release properties without any comparative studies are deemed to be speculative in nature. Applicant further argues that Hays provides no guidance relative to the amounts of cholesterol that would led to a liposome with intermediate release of a hydrophobic agent in regard to claim 25 and that although Hayes mentions negatively charged phospholipids, Hays does not teach or suggest lipids in claims 26 and 28. These arguments are not persuasive since Hays is suggestive of the use of cholesterol in 1 mole % and that the amounts of the negatively charged phospholipid can be varied depending upon factors such as the desired size and ***stability of liposomes in the blood stream***. With regard to applicant's arguments that Hays does not teach or suggest lipids in claims 26 and 28, the examiner points out that the rejection is made on the combination of references and Hersch is suggestive of the use of the lipids in claim 26 and 28. Applicant's arguments that Allen, Fujii or O'Rear discuss the inclusion of cholesterol within liposomes but do not teach or suggest the preparation of intermediate release liposomes are not persuasive since these references are suggestive of cholesterol function in the liposomes and that of O'Rear in particular teaches that various liposomes can be selected for the desired characteristics or manipulated to produce the desired characteristics and solute retention by liposomes and their half-life in the circulation can be controlled by appropriate manipulation of the liposomal membrane fluidity and

composition. Therefore, one of ordinary skill in the art would be motivated to vary the amounts of cholesterol to obtain the desired half-life of the drug.

8. Claims 27, 42, 47, 52, 57 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayes (5,869,092) alone or in combination with Hersch (5,759,571), Allen (BBA), Fujii (5,328,678), O'Rear (5,503,850) individually or in combination as set forth above, further in view of Anaissie (4,999,199).

The teachings of Hayes and other references have been discussed above. What is lacking in Hayes is the teaching that the phospholipid used in the liposome formation be DOPC.

Anaissie while disclosing liposomal formulations containing polyene antibiotics teaches that either DEPC or DOPC can be used (abstract, col. 7, lines 20-28).

The use of DOPC instead of DEPC taught by Hayes would have been obvious to one of ordinary skill in the art since Anaissie teaches the equivalency between these two phospholipids in liposomal formulations.

Applicant's arguments have been fully considered, but are not persuasive. The examiner has already addressed applicant's arguments with regard to Hayes, Hersch, Allen, Fujii and O'Rear. Applicant argues that Anaissie does not teach or discuss liposomes with intermediate release properties or liposomes with an elimination half-life range as described in the rejected claims and therefore does not remedy the deficiencies of Hayes alone or in combination with Hersch, Fujii, or O'Rear. These arguments are not persuasive since Anaissie is added to show the equivalency between

DOPC instead of DEPC and applicant has not shown any unexpected results by substituting DEPC with DOPC.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore/
Primary Examiner, Art Unit 1612

GSK